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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,410	05/29/2007	Deborah Hurst	51920-US-NP02	5534

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,410	HURST ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8, 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant cancels claims 2-5, 9-12.

Accordingly, claims 1, 6-8, 13-15 are examined in the instant application.

Withdrawn Rejection

The following rejections have been withdrawn: 1) 112, second paragraph and 112, first paragraph, scope, in view of the amendement, and 2) 103 rejection in view of the arguments and replaced with a new 103 rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-8, 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wierda et al, 2001, Expert Rev Anticancer Ther, 1(1): 73-83, IDS of 4/19/07, in view of Dmoszynska et al, 1999, Leukemia & Lymphoma, 34(3-4): 335-340, IDS of 04/17/09, and Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract only, of record, an further in view of Mark et al (US 4,518,584, filed on 12/20/1983), and as evidenced by the instant specification (p.3).

Claims 1, 6-8, 13-15 are as follows:

1. (Currently amended) A method of treating chronic lymphocytic leukemia in a human subject, said method comprising administering to said subject at least one cycle of concurrent therapy with an anti-CD52 antibody and an interleukin-2 (IL-2), wherein said IL-2 is des-alanyl-1, serine 125 human interleukin-2 and said anti-CD52 antibody is Alemtuzumab.

6. (Currently amended) : The method of claim 1, wherein said cycle comprises administering a therapeutically effective dose of the anti-CD52 antibody according to a weekly, twice weekly, or thrice-weekly dosing schedule in combination with administration of a constant IL-2 dosing regimen, said constant IL-2 dosing regimen comprising administering a total weekly dose of an the IL-2 to said subject.

7. (Currently amended) The method of claim 6, wherein a first dose of the IL-2 is administered to said subject concurrently with a first dose of the anti-CD52 antibody.

8. (Currently amended) The method of claim 7, wherein a first dose of the IL-2 is administered to said subject one week after a first dose of the anti-CD52 antibody is administered to said subject.

13. (Original) The method of claim 6, wherein one or more subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody is initiated about 1 month to about 6 months following completion of a first cycle or completion of any subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody.

14. (Original) The method of claim 13, wherein T-cell counts are monitored in said subject to determine when each of said cycles is initiated, said cycles being initiated when T-cell count is less than 80% of the T-cell count at the conclusion of any previous cycle of concurrent therapy with an IL-2 and an anti-CD52 antibody.

15. (Currently amended) The method of claim 6, wherein said total weekly dose of an IL-2 is in an amount that provides at least 50% of the NK stimulatory activity of a total weekly dose of Aldesleukin administered in a range of from about 1100 ug to about 2565 ug.

Wierda et al teach treating **chronic lymphocytic leukemia** (CLL) with monoclonal antibody **campath-1H, a humanized anti-CD52 antibody** thrice weekly up to 12 or 18 weeks (p.76). Wierda et al teach defective T-cell or NK-cell mediated immunity in CLL patients (p.74), and that there is concern for further immunosuppression in patients treated with campath (p.76, second column, last paragraph). Campath-1H is the same as Alemtuzumab as evidenced by the specification (p.3).

Wierda et al do not teach: 1) a combination of anti-CD52 antibody and interleukin-2 (IL-2) for treating CLL, 2) IL-2 is des-alanyl- 1, serine 125 human interleukin-2, 3) administration of CD52 antibody weekly or twice-weekly, and a total weekly dose of IL-2, 4) administration of anti-CD52 antibody and IL-2 by separate, sequential or simultaneous administration, or administration of a first dose of an IL-2 concurrent with or one week after a first dose of an anti-CD52 antibody and 5) initiation of one or more subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody at about 1 month to about 6 months following completion of a first cycle or completion of any subsequent cycles of concurrent therapy with IL-2 and anti-CD52 antibody, 6) T-cell counts are monitored in the subject to determine when each of said cycles is initiated, said cycles being initiated when T-cell count is less than 80% of the T-cell count at the conclusion of any previous cycle of concurrent therapy with an IL-2 and an anti-CD52 antibody and 7) total weekly dose of an IL- 2 is in an amount that provides at least 50% of the NK

stimulatory activity of a total weekly dose of Aldesleukin administered in a range of from about 1100 ug to about 2565 ug.

Dmoszynska et al teach that: 1) administration of low dose (100 ug daily for 6 weeks) of **IL-2** induces a marked increase in T cell subsets and NK cells in CLL patient treated with 2-chlorodeoxyadenosine (2CdA) (abstract, p.337 and Tables II-III on p.337, first column, p.336, first column), wherein treatment with 2CdA alone induces profound, long lasting suppression of CD4+ and CD8+ T lymphocytes in (p.335, first column), 2) IL-2 is given between the courses of 2CdA, in which patients are given 3-6 cycles of 2CdA (p.336, first column), and 3) the level of T cells and NK cells is not significantly different from initial IL-2 treatment after 6 weeks, as taught by Dmoszynska et al (Table III on page 337, columns II and III, and p.337, first column).

Denis-Mize et al teach that a combination with IL-2 would improve the efficacy and durability of anti-cancer monoclonal antibody therapy (abstract, first two lines). Denis-Mize et al teach that interleukin-2 (**Aldesleukin**), which is used in combination with rituximab in phase I clinical trail of Non-Hodgkin's lymphoma, acts by increasing T cells and NK activity, such as NK-mediated antibody dependent cellular cytotoxicity (ADCC) and cytolytic killing (abstract).

Mark et al teach making an IL-2 variant, **des-alanyl-1, serine 125 human interleukin-2**, where alanyl-1 is deleted and cysteine 125 is replaced with serine to eliminate intermolecular crosslinking or incorrect intramolecular disulfide bond formation (claim 4, and column 3, paragraph under "Modes for carrying out the invention""). Mark et al teach that des-alanyl-1, serine 125 human interleukin-2 (pLW46) has a higher IL-2 activity that of the native IL-2 control (column 18, Table II).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to combine the humanized anti-CD52 antibody, Campath1-H, taught by Wierda et al with interleukin-2 taught by Dmoszynska et al or Denis-Mize for treating CLL, because of the following reasons:

1) CLL patients have defective T-cell or NK-cell mediated immunity as taught by Wierda et al, which defective immunity is further suppressed by treatment with Campath, as taught by Wierda et al.

2) IL-2 increases T cells and NK activity in a combination therapy of IL-2 with the antibody rituximab in lymphoma patients, as taught by Denis-Mize or in a combination therapy of IL-2 with 2CdA in CLL patients, as taught by Dmoszynska et al.

Further, it would have been obvious to replace wild type IL-2 taught by Dmoszynska et al or Denis-Mize with the mutant des-alanyl-1, serine 125 human interleukin-2, taught by Mark et al, for enhancing the efficacy of treatment CLL, because des-alanyl-1, serine 125 human interleukin-2 is more advantageous than native IL-2, i.e., having higher IL-2 activity than native IL-2, in view of the teaching of Mark et al.

It would have been obvious to initiate subsequent cycle of treatment after the T-cell count is less than 80% of the T-cell count at the conclusion of any previous cycle of concurrent therapy with an IL-2 and an anti-CD52 antibody, because to maintain the level of T cells induced by initial IL-2 treatment, in view of the teaching of Dmoszynska et al.

Further, it would have been obvious to use a weekly dose of the mutant IL-2 taught by Mark et al, that provides at least 50% of NK stimulatory activity as provided by a weekly dose of

wild type IL-2 taught by Dmoszynska et al, to assure that at least 50% of NK activity is produced by the mutant Il-2 for treating CLL.

Concerning the frequency, the concentration and how anti–CD52 antibody and the mutant IL-2 are administered relative to each other, determination of optimum conditions is within the level of one of ordinary skill in the art. To determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Conlusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
February 9, 2010

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643